

## Immunology and cancer: gender differences

Anna Maria Di Giacomo, Michele Maio

Center for Immuno-Oncology, University Hospital of Siena, Italy

### Cancer immunotherapy, a very long-standing concept

The concept that immunotherapy could be useful in the treatment of cancer is a long-held hope coming from the observation that patients with cancer who developed bacterial infections experienced remission of their malignancies. The earliest mention of cancer-fighting infections dates to a citation from Ebers papyrus (1550 B.C.) attributed to the Egyptian physician Imhotep (2600 B.C.), who recommended to treat tumors (swellings) with a poultice followed by an incision which would result in infection of the tumor and therefore its regression. In 1896, the surgeon William Coley locally injected streptococcal broth cultures to induce erysipelas in an Italian patient (Mr. Zola) with an inoperable neck sarcoma, obtaining a tumor regression. Although therapy was toxic, the patient's tumor ultimately regressed, and he lived disease-free for 8 years before succumbing to his cancer.

### The cancer immunoediting concept

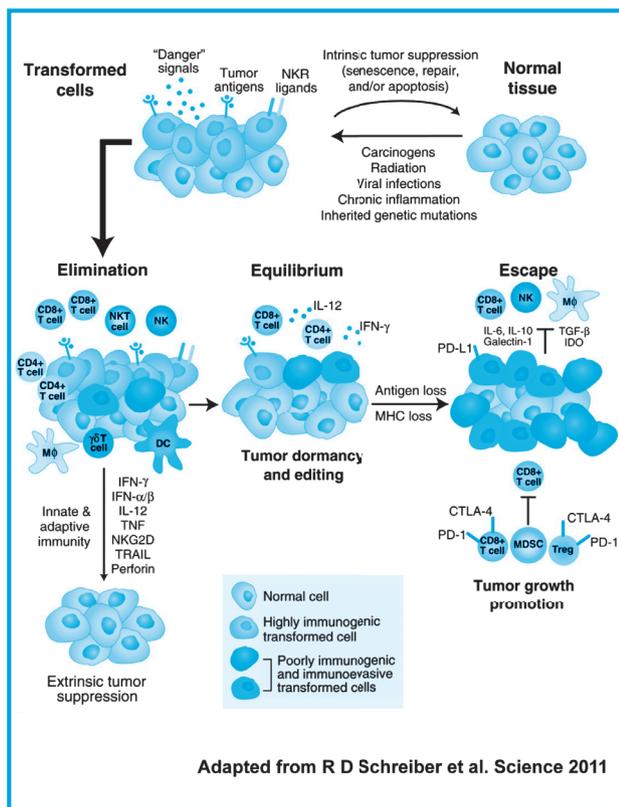
Cancer immunoediting is an extrinsic tumor suppressor mechanism that engages only after cellular transformation has occurred and intrinsic tumor suppressor mechanisms have failed. In its most complex form, cancer immunoediting consists of three sequential phases: elimination, equilibrium, and escape. In the elimination phase, innate and adaptive immunity work together to destroy developing tumors long before they become clinically apparent. Many of the immune molecules and cells that participate in the elimination phase have been identified, but more work is needed to determine their exact sequence of action. If this phase goes to completion, then the host remains free of cancer, and elimination thus represents the full extent of the process. If, however, a rare cancer cell variant is not destroyed in the elimination phase, it may then enter the equilibrium phase, in which its outgrowth is prevented by immunologic mechanisms. T cells, IL-12, and IFN- $\gamma$  are required to maintain tumor cells in a state of functional dormancy, whereas NK cells and molecules that participate in the recognition, or effect, or function of cells of innate

immunity are not required; this indicates that equilibrium is a function of adaptive immunity only. Editing of tumor immunogenicity occurs in the equilibrium phase. Equilibrium may also represent an end stage of the cancer immunoediting process and may restrain outgrowth of occult cancers for the lifetime of the host. However, as a consequence of constant immune selection pressure placed on genetically unstable tumor cells held in equilibrium, tumor cell variants may emerge that (i) are no longer recognized by adaptive immunity (antigen loss variants or tumor cells that develop defects in antigen processing or presentation), (ii) become insensitive to immune effector mechanisms, or (iii) induce an immunosuppressive state within the tumor microenvironment. These tumor cells may then enter the escape phase, in which their outgrowth is no longer blocked by immunity. These tumor cells emerge to cause clinically apparent disease (Figure 1)<sup>1</sup>.

### The Immune-checkpoint-based immunotherapy

The physiologic homeostasis of immune responses is controlled both by co-stimulatory (agonistic) and co-inhibitory (antagonistic) signals delivered by cell surface receptors belonging mainly to the immunoglobulin-like superfamily or to the tumor necrosis factor receptor superfamily<sup>2</sup>. Therefore, therapeutic mAb to agonistic or antagonistic immune check-points have been generated due to their potential to enhance anti-tumor immunity. Among co-stimulatory receptors in clinical development are OX40 and CD137, while CTLA-4 and PD-1 are among the co-inhibitory ones (Figure 2). Treatment with mAb to CTLA-4 or to PD-1/PD-L1, as well as their combination, has already shown significant clinical activity across a wide range of tumor types (i.e., melanoma, NSCLC, renal cell carcinoma, being under clinical development in the majority of solid and hemopoietic malignancies<sup>3</sup>. In light of these meaningful clinical results several studies aim to assess the role of different clinical and tumor molecular features that could help identifying the best candidates to immunotherapy.

Among these, tumor burden, molecular subtyping, age, and gender were evaluated to define their potential

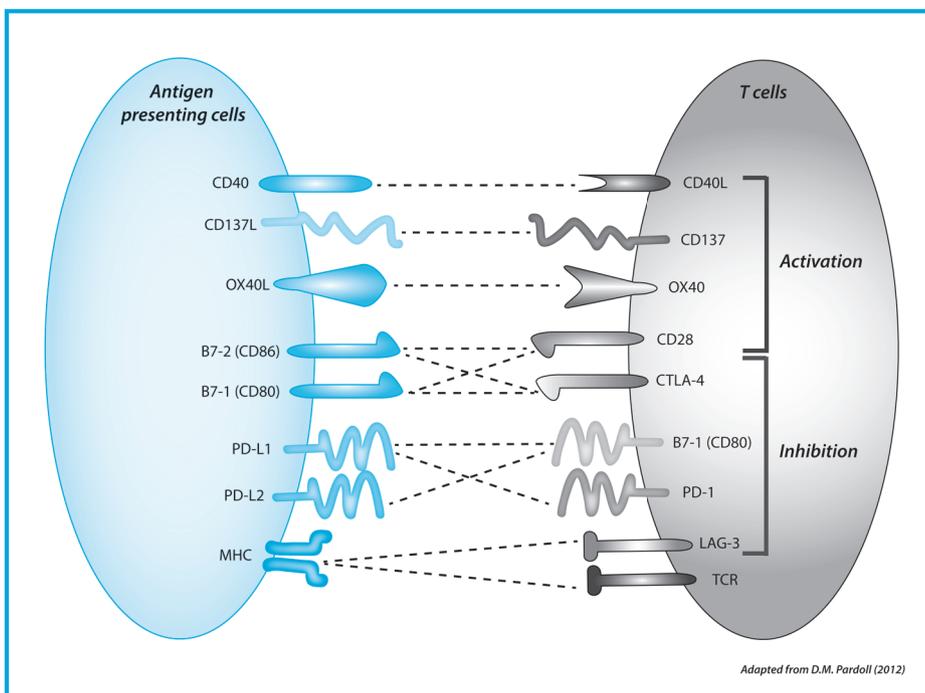


role in patient's selection. To date, the available retrospective subgroup analyses performed in several clinical studies conducted in different tumor histotypes (melanoma, NSCLC, RCC, etc.), and with different immune-checkpoints inhibitors (anti-CTLA-4, anti-PD1/PDL1) have not reported statistically significant differences in age or gender. However, gender differences in immune-regulation of T cell response have been identified; thus, prospective clinical and translational studies are needed to define potential mechanism(s) involved in gender differences with regards to immunotherapy. This could be also relevant to identify specific immunological targets to design studies exploring novel immunotherapy-based combinations, in different subgroups of cancer patients.

### References

1. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011; 331: 1565-70.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; 12 (4): 252-64.
3. Maio M, Di Giacomo AM. Immunologic checkpoints for cancer treatment: a continuing success. *Semin Oncol* 2015; 42 (3): 362.

**Figure 1.** The cancer immunoeediting concept.



**Figure 2.** T-cell checkpoint and co-stimulatory pathways.

*Correspondence to*  
**Anna Maria Di Giacomo**  
 Medical Oncology  
 and Immunotherapy  
 University Hospital of Siena  
 Viale Bracci, 14  
 53100 Siena, Italy  
 email a.digiacom@ao-siena.  
 toscana.it